

Concepts of establishing clinical bioequivalence of chlorofluorocarbon and hydrofluoroalkane β -agonists

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There are no established guidelines for judging equivalence between inhaled medications. The principles of establishing bioequivalence on the basis of bioavailability and pharmacokinetics may not be applicable to inhaled medications with predominantly topical and minimal systemic effects. For inhaled β_2 -agonists, the most practical method of showing in vivo therapeutic equivalence is by comparing relative potencies (RPs) of pharmacodynamic effects (bronchodilation and bronchoprotection). A range of doses that includes placebo should be studied in an appropriate design with adequate sample size, and relative potency should be estimated. Hydrofluoroalkane and chlorofluorocarbon salbutamol are bioequivalent for both their bronchodilator (RP, 1.08; 90% confidence interval, 0.95%, 1.23%) and bronchoprotective effects (RP, 1.08; 90% confidence interval, 0.81%, 1.46%) with similar safety profile. Eighteen subjects are required in a cross-over design to demonstrate bronchoprotective bioequivalence with a confidence interval of 67% to 150% for the relative potency (80% power). For salbutamol, this can be achieved with a comparison of 100 and 200 μ g doses. Twelve subjects would suffice for a cumulative dose-response study for bronchodilator bioequivalence. For both outcomes, repeatability and quality control of measurements have to be ensured for an accurate interpretation of the results. (*J Allergy Clin Immunol* 1999;104:S243-5.)

Key words: Bioequivalence, inhaled β -agonist

Metered dose inhalers (MDIs) containing chlorofluorocarbon propellants are the dominant delivery system for inhaled bronchodilators. Concerns about the depletion of the ozone layer by the catalytic action of the free chlorine radicals from the chlorofluorocarbons have led to legislation calling for the elimination of chlorofluorocarbon production.¹ Hydrofluoroalkanes, such as hydrofluoroalkane-134a, do not contain chlorine and are therefore environmentally friendly alternatives for use as propellants in the MDIs. They are known to be safe and efficacious as a substitute for chlorofluorocarbon-11/12 with β_2 -agonists like salbutamol and have already been licenced for clinical use (Proventil, Airomir).

Abbreviations used

CI:	Confidence interval
MDI:	Metered-dose inhaler
RP:	Relative potency

The new products were authorized for clinical use after a comparison was made of their in vitro and in vivo bioequivalence with that of the innovator salbutamol (Ventolin). If the test and reference products have the same galenic form and contain the same dose of the same active ingredient, they are said to be bioequivalent (when the profiles of the drug or metabolite, or both, are similar). The 3 principal in vivo methods currently available to study the bioequivalence of inhaled medications are radioaerosol drug deposition studies, pharmacokinetic studies, and comparative pharmacodynamic clinical efficacy studies.^{2,3} Although radioaerosol studies that use gamma scintigraphy provide useful information about lung deposition, their predictive ability for clinical efficacy of β -agonist is variable. Currently, no such studies have been performed to compare chlorofluorocarbon and hydrofluoroalkane salbutamol. Pharmacokinetic studies are of limited value for inhaled medications because the doses administered are small and the resulting serum concentrations are often too low to assay accurately. Furthermore, serum concentrations may not correlate with the dose delivered to the lung. A urine assay of salbutamol has been described⁴; however, there is no chlorofluorocarbon-hydrofluoroalkane bioequivalence data in subjects with asthma. Clinical efficacy studies are ultimately the most clinically useful measure of the effectiveness of inhaled β -agonist.

β_2 -agonists have 2 distinct pharmacodynamic effects of clinical importance in asthma: bronchodilation and prevention of bronchoconstriction.⁵ Both of these responses are clinically and physiologically distinct and important. Most in vivo bioequivalence studies of β_2 -agonists, including hydrofluoroalkane-salbutamol, have compared the bronchodilator action of different drugs. The nonbronchodilator effects may be studied by a comparison of the protection against bronchoconstriction caused by direct agents like methacholine⁶ or indirect agents like histamine,⁷ exercise, cold air, or allergen. Demonstration of the bioequivalence of bron-

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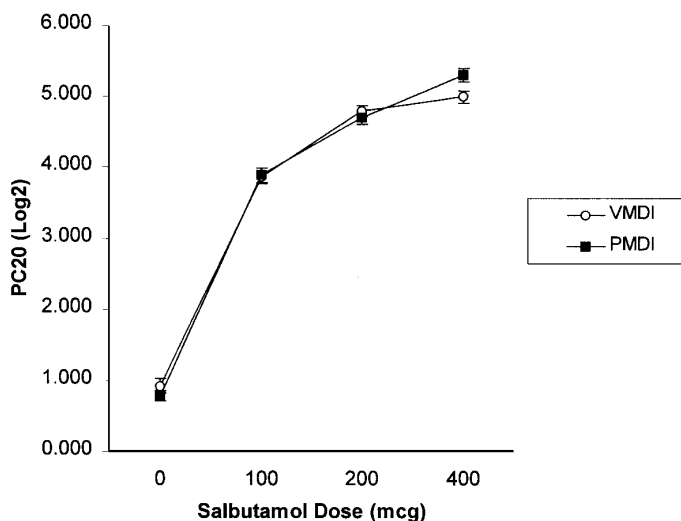


FIG 1. Dose-response curves of salbutamol (micrograms) plotted against PC₂₀ methacholine (log₂) for Proventil-hydrofluoroalkane (PMDI) and Ventolin-chlorofluorocarbon (VMDI).

choprotective effect is particularly important in patients with mild asthma who have minimal or no air-flow obstruction and in whom it might be difficult to compare the FEV₁ values. There are some recommendations for the bronchodilator studies, but none for conducting or analyzing the relative potencies of the bronchoprotective effects.

DESIGN AND METHOD ISSUES OF BIOEQUIVALENCE STUDIES

The British Association of Lung Research has made some recommendations as to how bronchodilator studies should be conducted.² The studies should be performed in patients with asthma, ideally with a range of severity. A range of doses should be compared in a placebo-controlled trial to establish a dose-response curve. The doses that are compared should be on the steep portion of the curve. The patients should be educated in proper inhalation technique. Comparisons should be made under conditions when inhalers are primed and unprimed. The outcome measure, whether it is FEV₁ (bronchodilation) or PC₂₀ (bronchoprotection), should be repeatable. In addition, for bronchoprotection studies, the concentration of methacholine or histamine should be stable during the period of the study. As with any controlled trials, the studies should have a large enough sample size to make meaningful interpretations. Currently, there are no recommendations as to what constitutes an appropriate sample size. The bioequivalence of clinical efficacy should be reported as relative potency (RP), calculated preferably by bioassay (Finney method).⁸ The US Food and Drug Administration considers 2 inhaled formulations as bioequivalent if the 90% confidence interval (CI) of the RP is between 0.67 and 1.50.

BRONCHODILATOR BIOEQUIVALENCE AND SAFETY

Several studies have reported the bioequivalence and safety of chlorofluorocarbon and hydrofluoroalkane salbutamol for its bronchodilator effect. In a cumulative dose-response study of 24 patients with asthma,⁹ the RP of the bronchodilator effect (percent of change in FEV₁) was reported as 1.08 (90% CI, 0.95, 1.23). A post-hoc power calculation with Monte-Carlo simulations of the ratio of the root mean square of the dose effect and slope of the dose-response curve showed that the study had 80% power to estimate RP with a 90% CI of 0.80 to 1.25. Bronchodilator bioequivalence has also been demonstrated in a placebo-controlled, 6-period, cross-over study in 26 patients with asthma.¹⁰ The safety of hydrofluoroalkane salbutamol compared with chlorofluorocarbon salbutamol has been demonstrated in short- and long-term randomized controlled double-blind studies¹¹ and has been confirmed in a recent UK postmarketing surveillance.

BRONCHOPROTECTIVE BIOEQUIVALENCE

Several studies have compared the bronchoprotective effects of 2 different formulations or delivery devices of β_2 -agonists.^{6,7,12} However, they have not been rigorous in the methods. Of particular importance are the lack of a range of doses, demonstration of a dose-response, lack of quality control of histamine or methacholine, and lack of standardization of the inhalation technique. Jenkins¹³ has reported that a single dose of chlorofluorocarbon and hydrofluoroalkane are bioequivalent for their bronchoprotective effect; however, single dose comparisons do not allow the calculations of RP. Ahrens et al¹⁴ have compared 2 doses of a chlorofluorocarbon and hydrofluoroalkane salbutamol

and demonstrated their bioequivalence for the bronchoprotective effect. The dose-response was not demonstrated, and the choice of doses was not justified.

We have recently compared the bronchoprotective effects of 3 doses (100, 200, and 400 μ g) of chlorofluorocarbon and hydrofluoroalkane salbutamol in 18 patients with mild asthma, in a randomized, placebo-controlled, dose-level blind, cross-over study.¹⁵ We made every effort to control factors that might influence the dose delivered to the airways, the interpretation of the methacholine PC₂₀, and consequently the results of the study. Patients were mild asthmatics with a PC₂₀ of less than 4 mg/mL with a demonstrable increase in PC₂₀ after 200 μ g of salbutamol, which would enable us to demonstrate a difference, if any, on the bronchoprotective effect between formulations. Dose-response curves may differ for patients with more severe asthma or heightened responsiveness. We excluded current or ex-smokers and patients who had recent upper respiratory tract infections and who had an FEV₁ of less than 70% of their predicted value, because these factors could increase the variability of methacholine responsiveness. The patients were educated in proper inhalation techniques, which were checked at every visit. Both the inhalers were primed an equal number of times before use to ensure optimum drug delivery during the study. We selected a range of doses that are routinely used in clinical practice to establish a dose-response curve. Because the bronchoprotective effect of methacholine bronchoconstriction was our main outcome measure, we ensured that the concentration of methacholine used was accurate and that it was stable during the period of the study. RP was estimated by Finney bioassay after the determination that the dose-response curves (Fig 1) were parallel and by an E-max model. The RP (90% CI), estimated by the Finney method with the 100, 200, and 400 μ g data was 1.08 (0.81,1.46). To compare the precision of this estimate with other estimates with only 2 doses, RP was also calculated with 3 different pairs of dosages: 100, 200; 100, 400; and 200, 400. The narrowest CI, which indicated the most precise estimate, was obtained with the 100 and 200 doses. The RP (90% CI) obtained by the E_{max} model (ED₅₀ for Proventil-hydrofluoroalkane and Ventolin-chlorofluorocarbon, 0.63 and 0.66, respectively) was 1.05 (0.71, 1.39). The changes in heart rate and systolic and diastolic blood pressures with the different doses of both drugs were not clinically or statistically significant. There were no significant adverse events to methacholine.

Post-hoc power calculation with Monte-Carlo simulations of the s/b ratio (0.39, where s = the root square mean error of the dose effect from the ANOVA model of dose-response analysis and b = the slope of the dose-response curve) gave us an 80% power to detect RP with a 90% CI of 0.67 to 1.50. Fifty-one patients would have given a more precise estimate (narrower 90% CI of 0.80 to 1.25). Analysis of the cumulative bronchodilator data from Kleerup et al⁹ suggests that only 28 patients are required to estimate the RP for the bronchodilator effect with similar precision. This result, plus the easier design, suggests that this design is the preferred method.

SUMMARY

The relative potencies of short-acting β_2 -agonists can be determined by comparing their bronchodilator and bronchoprotective effects. With the Finney bioassay method, hydrofluoroalkane and chlorofluorocarbon salbutamol are bioequivalent for both the clinical effects. Two doses (100 and 200 μ g) of salbutamol MDI in 18 patients with asthma are sufficient to establish bronchoprotective bioequivalence with 80% power. Bronchodilator bioequivalence can be demonstrated with the same precision with a fewer number of subjects in a cumulative dose-response design.

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